REMARKS

Claims 1-17, 23, and 25-35 are pending in the application. Claims 1-5, 10-17, and 23 are currently under examination, and claims 6-9 and 25-28 are withdrawn as directed to non-elected subject matter.

With this response, claims 1, 3-5, 25, 26, and 29-31 are amended to more clearly define the claimed subject matter. Claims 6-9, 27, and 28 are canceled, and new claims 36-39 are presented. Support for the added language "ameliorate a symptom" in claims 1 and 3-5 can be found in the specification at page 9, ¶ 30, for example. Support for the amendment to claims 29-31 can be found in the specification at page 15, ¶ 47, and support for newly added claims 36-39 can be found throughout the specification and at original claim 4. Thus, no new matter is added by this amendment.

Applicants thank Examiner Turner for extending them the courtesy of a telephonic interview today. In the interview, the participants discussed and clarified the pending enablement rejections. Applicants believe that this response is fully responsive to the pending rejections of the claims as allegedly non-enabled and inadequately described.

In the pending Office Action, the Examiner enters the amendment submitted on March 6, 2006 to add new claims 29-35, and then requires restriction of these claims, alleging that they are distinct from the "invention" of elected Group I. Applicants traverse the restriction of claims 29-35. Applicants believe the restriction between these claims and Group I is improper because the Examiner has not shown that it would be a

serious burden to examine the claims together with the elected claims of Group I, nor has the Examiner shown how the claims are independent or distinct.

Group I is defined in the Office Action dated January 4, 2006 as claims drawn to methods for treating or preventing at least one degenerative disorder of muscle, bone, or glucose homeostasis comprising administering an ActRIIB-Fc fusion protein. Group I includes claim 1, and as amended, claims 1 and 29-35 are drawn to ameliorating a symptom of a degenerative disorder of muscle. Thus, all claims relate to methods of treating the same degenerative disorders by administration of the same fusion protein. These claims are related both structurally and functionally. As a result, claims 29-35 could all be examined with a single search in conjunction with Group I. See M.P.E.P. § 802. Applicants thus respectfully request that the restriction requirement as to claims 29-35 be withdrawn.

Claim Rejections - 35 U.S.C. § 112

The Examiner has rejected claims 1-5, 10-17, and 23 as allegedly lacking enablement and written description under 35 U.S.C. § 112, first paragraph.

Enablement

The Examiner rejects the pending claims as allegedly lacking enablement, and argues that the specification does not enable one skilled in the art to practice the claimed methods. Independent claim 1 is directed to a method for ameliorating a symptom of a degenerative muscle disorder by administering an ActRIIB fusion polypeptide that is at least 95% identical to amino acids 23-138 of SEQ ID NO:3. The Examiner alleges that the specification is not enabling because it does not teach which

residues of the claimed ActRIIB polypeptides can be modified such that the protein maintains functionality.

Applicants respectfully submit that the specification enables the full scope of polypeptides recited in each of the amended claims. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976). Furthermore, the skilled artisan need not be able to predict which structures will retain function; trial and error experimentation is not necessarily undue. See, e.g., In re Wands, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation).

In the instant case, the claims as amended are enabled because the specification and knowledge in the art provide ample guidance as to changes that could be made to the ActRIIB sequences without disrupting its GDF-8 binding activity. In addition, any experimentation that would need to be done would not be undue. In fact, guidelines for producing variants likely to retain GDF-8 binding activity were known to those of skill in the art and are referenced, for example, at page 17, lines 3-20.

Furthermore, a protein that falls within the scope of the claims has two characteristics that are easily determined by one of skill in the art. First, the protein must be an ActRIIB fusion polypeptide comprising a sequence at least 95% identical to amino acids 23 to 138 of SEQ ID NO:3. Determining which proteins have this property simply requires sequencing the encoding DNA or the protein itself, both of which are routine tasks. Second, the protein must bind to GDF-8. Protein binding assays are routine and well within the skill of those in the art, and the specification teaches how to

perform such GDF-8 binding assays, for example, at Examples 5 and 6 and Figure 1. Additionally, receptor-ligand binding assays, and in particular, GDF-8 binding assays, were known in the art at the time of filing, and methods for performing them were described in the literature (Lee and McPherron, *Proc. Natl. Acad. Sci. USA*, 98:9306-11 (2001)). Based on the disclosure in the specification, and the knowledge of those skilled in the art at the time of filing, the experimentation involved in selecting an ActRIIB fusion protein with 95% identity to amino acids 23 to 138 of SEQ ID NO:3 that maintains its ability to bind to GDF-8 when altered does not rise to the level of "undue experimentation", as analyzed under the factors of In re Wands, 858 F.2d 731 (Fed. Cir. 1988). For example, the GDF-8 binding experiments do not constitute undue experimentation because the specification provides guidance in the working examples, the methods are predictable for determining receptor-ligand binding ability, and the level of ordinary skill within the art is high, as the field generally consists of advanced degree researchers.

Furthermore, Applicants respectfully submit that the state of the art at the time of filing provided significant guidance as to which residues of ActRIIB could be altered without disrupting its GDF-8 binding activity. ActRIIB is a member of the activin receptor family, and this family contains proteins with substantial sequence homology. The extracellular domain of activin receptor type II is 54% identical to the extracellular domain of activin receptor type II B (Attisano et al. *Cell* 68:97-108 (1992), Figure 4B). Additionally, the extracellular domains of activin type II receptors contain conserved cysteine residues that correspond with TGF-β type II receptors and these residues have been recognized as an important functional feature (Lin et al. *Cell* 68:775-785 (1992),

Figure 5B). Accordingly, one of skill in the art would have been aware, as of the filing of the present application, of residues or fragments of the ActRIIB protein that are highly conserved and thus potentially important for its GDF-8 binding function.

The Examiner further alleges that the specification does not provide support for methods to treat or prevent diseases of a degenerative disorder of muscle, bone, or glucose homeostasis.

Without acquiescing to the rejection, Applicants amend the claims to expedite allowance, and to more clearly set forth the claimed subject matter. In particular, claims 1 and 3 have been amended to claim degenerative disorders of muscle only. Furthermore, claim 4 has been amended to recite muscular dystrophy, Duchenne's muscular dystrophy, muscle atrophy, and muscle wasting syndrome.

It was known in the art from *in vivo* studies that skeletal muscle mass could be increased via inhibition of GDF-8 (McPherron et al., *Nature* 387:83-90 (1997); Bogdanovich et al., *Nature* 420:418-421 (2002)). Furthermore, it was known that GDF-8 antagonists could increase muscle mass and strength in a *mdx* mouse strain (Bogdanovich et al., *Nature* 420:418-421 (2002)). Thus, those skilled in the art, at the time of filing, would recognize that inhibiting GDF-8 would be useful in treating or preventing disorders related to muscle degeneration.

The Applicants have shown, using an *in vivo* murine model, that an ActRIIB fusion polypeptide inhibits GDF-8 and increases muscle mass (Example 9). The Applicants also show that ActRIIB is more effective than JA16 at increasing muscle mass in an *in vivo* mouse model (page 44, ¶ 114) (see also, Bogdanovich at page 419, and Figure 2, showing that JA16 increases muscle mass and strength in the *mdx*

mouse strain). Therefore, Applicants have enabled the claimed methods of ameliorating a symptom of a degenerative disorder of muscle (claim 1), of a muscle disorder or neuromuscular disorder (claim 2), of a disorder chosen from at least muscular dystrophy, Duchenne's muscular dystrophy, muscle atrophy, and muscle wasting syndrome (claim 4), as well as each of these disorders individually (claims 36-39). The claimed muscle disorders are linked by the common feature of having a symptom of decreased muscle mass, and since the Applicants have enabled a method of increasing muscle mass by administering ActRIIB fusion polypeptides, the claims are enabled.

The Examiner cites an article by Fabb et al. as evidence that an *in vivo* or *in vitro* model may only be used to establish enablement of method of treatment claims where predictability of the treatment may be shown. The Examiner contends that the Fabb article stands for the conclusion that an animal model of gene therapy is not predictive of success in human treatment, citing the following passage "long-term studies in immunocompetent mdx mice as well as in larger animal models are now required to further evaluate the potential of the gene therapy approach in the context of human disease." Office Action, page 6. Applicants respectfully submit that the Examiner has confused the scientific standard for proof and the legal standard required for enablement. Compliance with the enablement requirement does not require actual reduction to practice before filing, but rather a showing that the claimed result could be accomplished without undue experimentation. Gould v. Quigg, 822 F.2d 1071, 1078, (Fed. Cir. 1987); M.P.E.P. § 2164.02. An *in vivo* or *in vitro* animal model example is a "working example" for the purposes of the claimed treatment if the model "correlates

with" (not "is predictive of") the claimed treatment. M.P.E.P. § 2164.02. Applicants submit that the animal model of Example 9, showing an increase of muscle mass upon administration of an ActRIIB fusion protein, correlates with that same function in humans.

Additionally, Applicants note that the Fabb article is related to the use of gene transfer to affect muscle degeneration, which differs significantly from the claimed use of protein therapeutics. The Examiner has not provided any evidence that the difficulty in translating laboratory results from gene transfer experiments to their potential as therapeutics discussed in Fabb would apply to the claimed use of protein formulations as therapeutics.

Applicants respectfully submit that the claims are enabled by the specification as filed because the claimed methods of ameliorating a symptom of a degenerative muscle disorder by administering an ActRIIB fusion protein can be performed by the skilled artisan without undue experimentation. Thus, Applicants respectfully request that the rejection of the claims as lacking enablement under 35 U.S.C. § 112, first paragraph, be withdrawn.

Written Description

The Examiner rejects the pending claims under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the claims encompass fragments and homologs of ActRIIB polypeptides, and that the disclosure of a single polypeptide does not adequately

support the claimed genus of ActRIIB fusion proteins that are at least 95% homologous to amino acids 23 to 138 of SEQ ID NO:3, and exhibit the functional limitation of binding to GDF-8.

Applicants' support for the recited polypeptides exceeds the written description standard articulated by the PTO's own Guidelines. Example 14 of the Written Description Guidelines states that disclosure of a single protein sequence provides adequate written description support for the genus of proteins comprising sequences that are at least 95% identical to that sequence and catalyze the reaction of A to B. As in Example 14, the instant claims relate to a polypeptide comprising an amino acid sequence that satisfies a functional limitation (having GDF-8 binding activity) and a structural limitation (at least 95% identical to amino acids 23 to 138 of SEQ ID NO:3). As in Example 14, the specification and knowledge in the art provide procedures for making variants of the disclosed sequence and assays to identify variants satisfying the functional limitation (as described above).

Furthermore, an adequate written description of a DNA or protein requires a precise definition, such as by structure, formula, chemical name, or physical properties. Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993). The specification of the instant invention provides both structure and physical properties of the claimed genus. For example, as discussed above, the members of the claimed genus share the structural feature of having at least 95% homology to amino acids 23 to 138 of SEQ ID NO:3, and the physical property of being capable of binding to GDF-8. A polypeptide having 95% identity to amino acids 23 to 138 of SEQ ID NO:3 differs from the later by no more than six amino acids. One with skill in the relevant art would know how to identify such

members of the genus based on structure alone, which is provided in the specification at page 17, lines 3-20.

The Examiner states that the specification fails to teach any other polypeptide sequences capable of providing the same function, and that it also fails to teach the portion of the ActRIIB polypeptide required for GDF-8 binding. Applicants respectfully disagree. Having provided a clear structural limitation on the claimed genus, the specification also clearly defines the physical property of GDF-8 binding. By providing simple and routine assays for determining whether any given polypeptide can bind to GDF-8, the specification teaches those of skill in the art what polypeptides may be used in the claimed invention. In providing these structural and physical properties of the claimed genus, the specification is clearly describing possession of the genus as a whole. Accordingly, Applicants request withdrawal of the rejection of claims 1-5, 10-17, and 23 as lacking written description under 35 U.S.C. § 112, first paragraph.

Conclusion

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is in conformance with the enablement and written description requirements of 35 U.S.C. § 112. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: August 21, 2006

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